

Mechanism of multidrug resistance to chemotherapy mediated by P-glycoprotein (Review)

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Abstract. Multidrug resistance (MDR) seriously limits the clinical application of chemotherapy. A mechanism underlying MDR is the overexpression of efflux transporters associated with chemotherapeutic drugs. P-glycoprotein (P-gp) is an ATP-binding cassette (ABC) transporter, which promotes MDR by pumping out chemotherapeutic drugs and reducing their intracellular concentration. To date, overexpression of P-gp has been detected in various types of chemoresistant cancer and inhibiting P-gp-related MDR has been suggested. The present review summarizes the mechanisms underlying MDR mediated by P-gp in different tumors and evaluated the related signaling pathways, with the aim of improving understanding of the current status of P-gp-mediated chemotherapeutic resistance. This review focuses on the main mechanisms of inhibiting P-gp-mediated MDR, with the aim of providing a reference for the study of reversing P-gp-mediated MDR. The first mechanism involves decreasing the efflux activity of P-gp by altering its conformation or hindering P-gp-chemotherapeutic drug binding. The second inhibitory mechanism involves inhibiting P-gp expression to reduce efflux. The third inhibitory mechanism involves knocking out the ABCB1 gene. Potential strategies that can inhibit P-gp include certain natural products, synthetic compounds and biological techniques. It is important to screen lead compounds or candidate techniques for P-gp inhibition,

and to identify inhibitors by targeting the relevant signaling pathways to overcome P-gp-mediated MDR.

Contents

1. Introduction
2. MDR caused by P-gp in various tumor tissues
3. Signaling pathways involved in P-gp mediated MDR
4. Reversing MDR by inhibiting P-gp
5. Reversing MDR by inhibiting P-gp expression
6. Reversing MDR by silencing ABCB1 DNA
7. Conclusions and perspective

1. Introduction

With the development of medical science and technology, the diagnostic efficiency and treatment of cancer has markedly improved. There are three main types of systemic cancer treatments: Chemotherapy, targeted therapy and immunotherapy (1,2). There are notable individual differences in the therapeutic effects of targeted therapy and immunotherapy. Chemotherapy, which kills tumor cells indiscriminately, is considered an irreplaceable cancer treatment. Unfortunately, tumor multidrug resistance (MDR), resulting in the lack of tumor sensitivity to a number of chemotherapy drugs, is an obstacle limiting chemotherapy application (3). The mechanisms underlying MDR include ATP-binding cassette (ABC) transporter overexpression, autophagy, DNA damage repair, cancer stem cells, genetic mutations and DNA methylation (4-8). Overexpressed ABC transporters, which are the main cause of chemotherapy MDR, use the energy generated by ATP hydrolysis to pump chemotherapy drugs out of the cell (9). MDR-related ABC transporters include P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP) and lung resistance-associated protein (LRP). P-gp is the main cause of MDR in tumors according to numerous studies (10,11).

P-gp was the first drug resistance-related protein to be discovered. In 1976, P-gp was identified in drug-resistant Chinese hamster ovary cells as a membrane glycoprotein with a molecular weight of ~170 kDa (12). P-gp, encoded by

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the ABCB1 gene, is the most studied transmembrane transporter in the ABC transporter family. The structure of P-gp consists of two nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs) (13). NBDs are located in the cytoplasm and transfer energy through membranes to transport substrates. TMDs consist of six transmembrane α -helical structures that provide specificity for substrates. Chemotherapy drugs that act as P-gp substrates are pumped out of tumor cells (14,15).

P-gp has been reported to be overexpressed in various tumors, such as osteosarcoma, hepatocellular carcinoma (HCC) (16), breast cancer (17), gastric cancer (18), lung cancer (19,20) and bowel cancer (21), resulting in chemotherapy resistance. P-gp overexpression reduces intracellular drug concentrations and cytotoxicity by using its efflux pump function to expel cisplatin (20), paclitaxel (22), 5-fluorouracil (5-Fu) (23), doxorubicin (DOX) (24) and other chemotherapeutic drugs out of cells, which results in inadequate proliferation-inhibiting effects of chemotherapy drugs on tumor cells. In view of the common phenomenon of clinical chemotherapy resistance, a large number of studies have been carried out on the mechanism of P-gp-mediated chemotherapy resistance and P-gp inhibitors (25,26).

The present review aims to provide an overview of the overexpression of P-gp in different types of cancer leading to chemotherapy resistance (Fig. 1). This review summarizes and elaborates on three current strategies for overcoming P-gp-mediated chemotherapy resistance (Fig. 2). The first strategy involves competitive or noncompetitive suppression of the P-gp efflux pump function. The second strategy involves inhibition of the expression of P-gp and efflux transporters on the cell membrane that bind to chemotherapy drugs. The third approach involves knockout of the ABCB1 gene. The active substances that reverse P-gp-mediated chemotherapy resistance through these three pathways can also be classified into groups. They are roughly divided into natural products, synthetic compounds, endogenous RNAs and biological compounds. The present review aims to alert researchers to the important contribution of P-gp overexpression in chemotherapy resistance and to provide a reference for P-gp-related chemotherapy resistance research.

2. MDR caused by P-gp in various tumor tissues

Before the advent of targeted therapy and immunotherapy, chemotherapy was the most common clinical treatment for a variety of malignant tumors; therefore, P-gp is a common mechanism underlying MDR in multiple malignant tumors. In general, ABC transporters, including P-gp, are expressed more highly in resistant tumors, which increases the chance of drug efflux. The high expression of P-gp in liver cancer, lung cancer, breast cancer, bowel cancer, gastric cancer and osteosarcoma leads to chemoresistance.

MDR caused by P-gp in liver cancer. Liver cancer is a type of malignant tumor that can be caused by alcoholism, drug injury and viral infection (27). Before sorafenib, a small-molecule targeted drug, was approved by the United States Food and Drug Administration for the treatment of advanced HCC, chemotherapy was the preferred treatment for unresectable liver cancer (28).

P-gp overexpression-mediated MDR is sometimes induced by external factors and not the spontaneous behavior of cancer cells following prolonged exposure to chemotherapy drugs. HepG2 cells are resistant to DOX in an acute or chronic hypoxic environment, and have high expression levels of nuclear factor erythroid-2 related factor 2 (Nrf2) and P-gp. It has been hypothesized that hypoxia can induce the expression of P-gp by inducing the expression of Nrf2 (29).

The regulatory mechanism of P-gp is a multimolecular process. In DOX-resistant liver cancer cells, the levels of NF- κ B and P-gp are relatively high, thus indicating that the expression of NF- κ B in HCC may be closely related to the ABCB1 gene (16). It has also been reported that the resistance of HCC to epirubicin is associated with the high expression of tripartite motif protein 25 (TRIM25). Epirubicin-resistant HCC cells in which TRIM25 was knocked down have been shown to exhibit increased sensitivity to epirubicin, an increased apoptosis rate and downregulation of P-gp (30). Furthermore, Bcl-2-associated transcription factor 1 can promote 5-Fu resistance, and the expression of P-gp and MRP1 in HCC cells by directly binding to the promoter region of long non-coding RNA (lncRNA) NEAT1 (31).

MDR caused by P-gp in lung cancer. Lung cancer is one of the most life-threatening types of cancer (27). P-gp-mediated cisplatin resistance is prominent in lung cancer. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was first found in non-small cell lung cancer (NSCLC). It has been reported that upregulated MALAT1 in A549 NSCLC cells promotes P-gp expression and P-gp-mediated cisplatin resistance by increasing signal transducer and activator of transcription 3 (STAT3) phosphorylation levels (32). In addition, it has been confirmed that the mRNA stability of ABCB1 and STAT3 phosphorylation in lung cancer cells can be enhanced by sodium butyrate (SB); therefore, it can be inferred that P-gp expression may be positively mediated by SB-induced expression or phosphorylation of STAT3 (33). Chloride channel-3 (ClC-3) promotes ABCB1 and P-gp expression by activating the NF- κ B signaling pathway, and the key point of this process is the nuclear translocation of NF- κ B P65 (19). Furthermore, upregulation of hypoxia-inducible factor (HIF) in NSCLC may lead to P-gp overexpression and promote cisplatin resistance (20); this result is similar to the mechanism of hypoxia-induced P-gp overexpression in liver cancer. Therefore, it may be suggested that modulating oxygen supply to tumors could overcome P-gp-mediated MDR.

MDR caused by P-gp in osteosarcoma. Osteosarcoma is a highly malignant tumor with a poor prognosis; however, chemotherapy before and after surgery can greatly improve this prognosis (34). Previous studies have confirmed that P-gp expression is positively associated with MDR in osteosarcoma (11,35). The expression levels of P-gp in cisplatin-resistant osteosarcoma cells have been shown to be much higher than those in nondrug-resistant cells. Furthermore, following knockdown of P-gp expression, the sensitivity of osteosarcoma cells to cisplatin was restored (11). Pleiotrophin (PTN), a neurotrophic growth factor, is linked to DOX resistance caused by P-gp overexpression. PTN can upregulate ABCB1/P-gp by

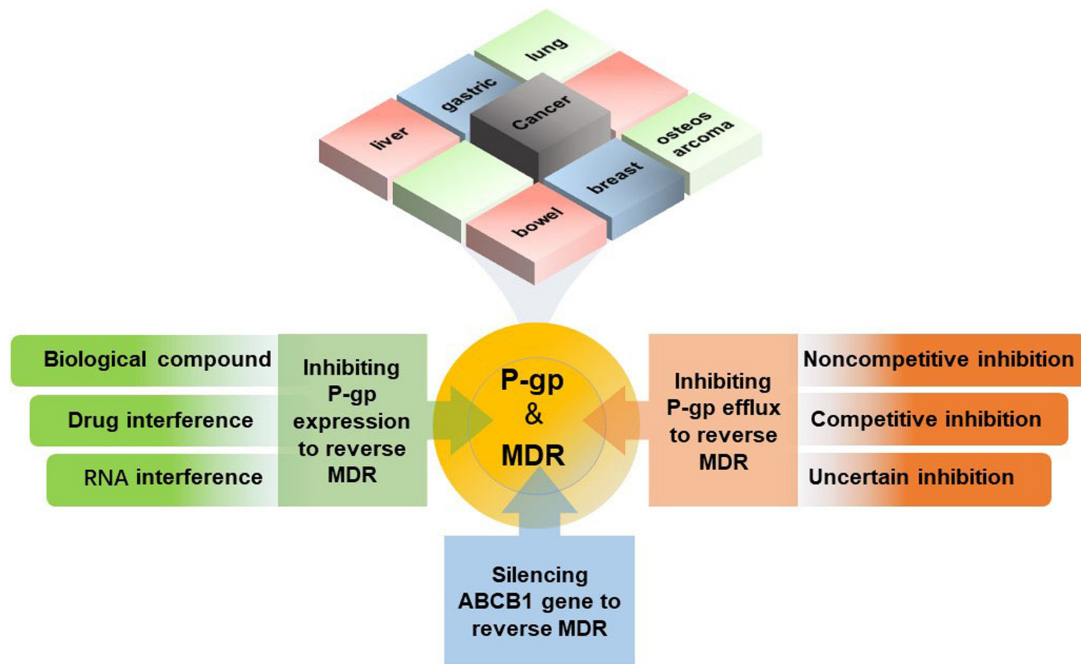


Figure 1. Overexpression of P-gp in liver cancer, lung cancer, breast cancer, gastric cancer, bowel cancer and osteosarcoma results in resistance to multiple chemotherapies. There are three ways to reverse P-gp-mediated resistance to chemotherapies: i) Inhibiting the efflux function of P-gp; ii) inhibiting P-gp expression; iii) silencing MDR genes. MDR, multidrug resistance; P-gp, P-glycoprotein.

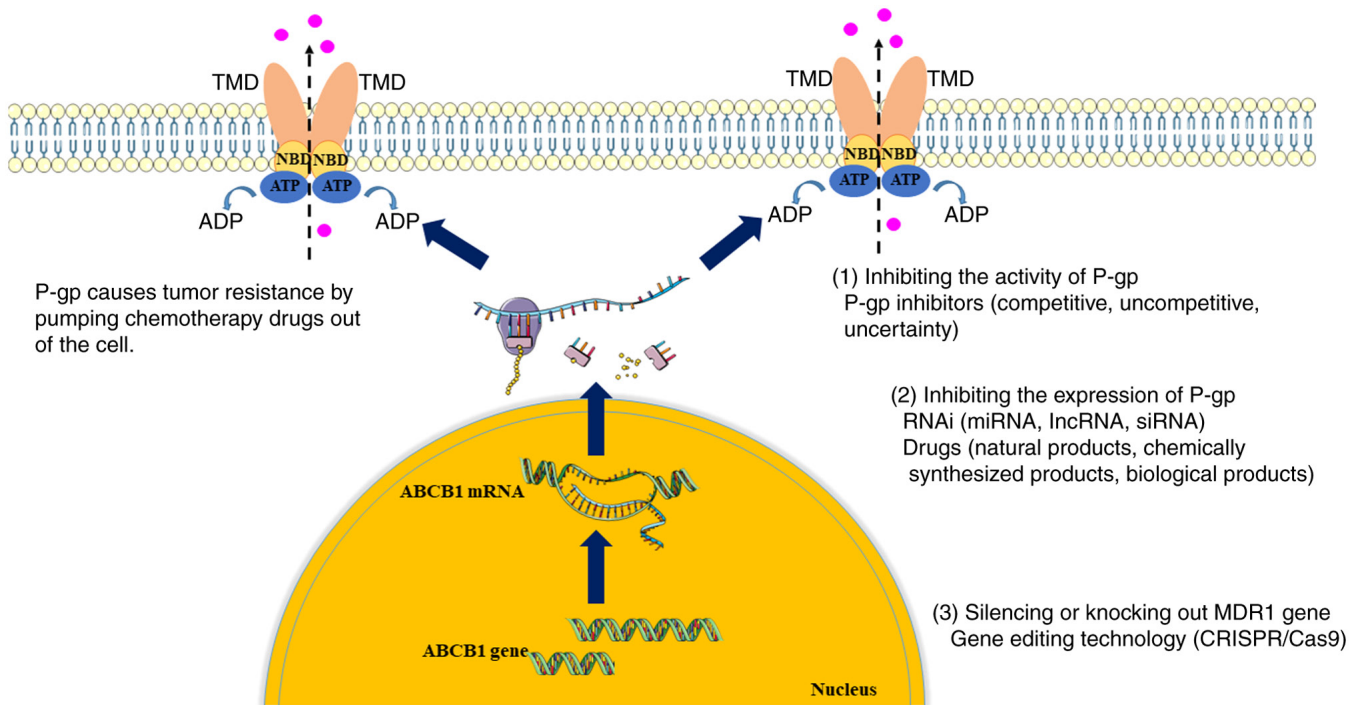


Figure 2. Upregulation of P-gp pumps chemotherapy drugs out of cells, reducing the intracellular concentration of chemotherapy drugs and leading to chemotherapy drug resistance. There are three ways to reverse P-gp mediated chemotherapy resistance: (1) Inhibiting the activity of P-gp; (2) inhibiting the expression of P-gp; (3) silencing or knocking out the ABCB1 gene. These ways increase the concentration of intracellular chemotherapy drugs and reverses resistance to chemotherapy drugs. MDR, multidrug resistance; P-gp, P-glycoprotein; NBD, nucleotide-binding domains; TMD, transmembrane domain; RNAi, RNA interference; miRNA, microRNA; lncRNA, long non-coding RNA; siRNA, small interfering RNA.

mediating ALK/GSK3 β / β -catenin signaling (35). LIM domain kinase 1 (LIMK1), a member of the serine/threonine protein kinase family, can also contribute to MDR by upregulating the levels of P-gp. This finding was demonstrated by transfecting

MG63/VCR osteosarcoma cells with LIMK1-small interfering RNA (siRNA), wild-type-LIMK1 or empty vector; the apoptosis rate of cells transfected with LIMK1-siRNA was higher (36).

MDR caused by P-gp in breast cancer. P-gp is associated with drug resistance to a variety of anticancer drugs used in the treatment of breast cancer. At present, there are two types of breast cancer resistance mechanisms related to P-gp: Activation of the P-gp efflux pump and enhancement of P-gp expression.

The interaction of programmed cell death ligand 1 (PD-L1) and programmed cell death-1 (PD-1) on T cells can enhance chemotherapeutic resistance in breast cancer cells by inhibiting immune responses (37). Therefore, the regulation of MDR by the tumor immune microenvironment was investigated. From the perspective of tumor autoimmune regulation, P-gp-mediated MDR may be an immune response to exogenous chemotherapy drugs. Activation of multiple signaling pathways promotes P-gp expression and MDR in breast cancer. Notably, activating PI3K/AKT and MAPK/ERK pathways can increase the expression of ABCB1/P-gp and enhance DOX resistance (37). ABCB1 transcription can also be directly promoted by WW domain-binding protein 2 through binding to ER α , which is a potential mechanism of P-gp-related MDR (38). Nkx-2.5, a transcription factor, can bind to the +4 to +10 binding site of the upstream promoter of ABCB1 in breast cancer cells, thereby transactivating ABCB1 for transcription. Eventually, P-gp is upregulated, thus leading to breast cancer resistance (39). In addition to studies regarding the increased expression of P-gp, β 1-integrin binding to collagen type 1 has been reported to induce chemoresistance of breast cancer cells by activating ABC efflux transporters (40).

Furthermore, resistance to trastuzumab emtansine, which is an antibody-conjugated drug used to treat metastatic breast cancer, is related to the upregulation of P-gp (41).

MDR caused by P-gp in gastric cancer. A number of studies on gastric cancer resistance have been conducted because of its high incidence (42,43). Notably, lncRNAs are closely related to the occurrence of P-gp-mediated gastric cancer resistance. The high expression of lncRNAs differentiation antagonizing non-protein coding RNA (DANCR) and gastric carcinoma proliferation enhancing transcript 1 (GHET1) in gastric cancer cells can increase the occurrence of drug resistance by upregulating the expression of ABCB1, which has been confirmed by silencing DANCR and GHET1 (44,45).

Zinc finger protein 139 inhibits the transcriptional activity of the microRNA (miRNA/miR)-185 promoter to downregulate miR-185, which also reduces the expression of ABCB1 (46). lncRNAs and miRNAs are non-coding RNAs transcribed from the genome that regulate epigenetics and signal transduction *in vivo*. Therefore, the involvement of lncRNAs and miRNAs in P-gp-mediated MDR is not surprising.

MDR caused by P-gp in bowel cancer. Chemotherapeutic resistance is also a vital obstacle in the clinical treatment of bowel cancer. Activation of the ABCB1 promoter region promotes P-gp expression and MDR. Visfatin regulates ABCB1 transcription by regulating ABCB1 promoter activity to mediate the DOX resistance of colorectal cancer cells. When transfected with visfatin-specific siRNA, the expression of ABCB1 in colorectal cancer cells was significantly reduced and the sensitivity to DOX was restored (47). ABCB1 mRNA and protein expression can be stimulated by forkhead box O3

through binding to the promoter region of ABCB1, and the proliferation of colon cancer cells and MDR can be induced by the overexpression of forkhead box O3 (48). In addition, IL-8 is significantly upregulated in DOX-resistant colorectal cancer cells. Notably, NF- κ B (P65) may be activated by IL-8 via upregulation of IKK β phosphorylation, thus resulting in overexpression of P-gp (49). P-gp expression can also be promoted by SET and MYND domain-containing protein 2 through the MEK/ERK/AP-1 signaling pathway, leading to the resistance of colon cancer to oxaliplatin (21). A relationship also exists between ABCB1 and adhesion G protein-coupled receptor G1 (GPR56), a type of adhesion G-protein coupled receptor. GPR56 can enhance drug resistance through upregulation of ABCB1 levels via a RhoA-mediated signaling mechanism in primary colon tumors (50).

3. Signaling pathways involved in P-gp mediated MDR

P-gp exerting its efflux pump function is the final step leading to chemotherapy MDR. Considering the large number of molecules in the body, P-gp-mediated MDR is likely to be regulated by a variety of signaling pathways (Fig. 3) P-gp overexpression mediates MDR in various types of cancer and the signaling pathways involved are similar. These pathways may seem intricate, but they all contain the same key molecule, NF- κ B, which acts as a hub. Simultaneous overexpression of NF- κ B and P-gp in drug-resistant tumors has prompted studies on the regulation of P-gp by NF- κ B (51,52). The positive regulatory effect of NF- κ B on P-gp has been verified by comprehensive analysis of the signaling pathway of P-gp inhibitors (16). It has been reported that NF- κ B regulates P-gp through the downstream STAT3 signaling pathway and the regulation of NF- κ B on P-gp is influenced by a number of upstream molecules in the body. N-acetyl-glucosaminyl transferase III can inhibit DOX resistance by negatively regulating P-gp expression through the TNFR2-NF/ κ B signaling pathway (53). Furthermore, melatonin inactivates the NF- κ B pathway and downregulates P-gp, thus increasing sensitivity to epirubicin chemotherapy (54). By contrast, IL-8 positively regulates P-gp expression in DOX-resistant cells by activating the IKK β /NF- κ B signaling pathway (49). CIC-3 also increases ABCB1 mRNA and P-gp levels by activating the NF- κ B signaling pathway (19).

Dysregulation of the PI3K/Akt signaling pathway, which is commonly seen in cancer, and regulates metabolism, proliferation, cell survival, growth and angiogenesis, has also been reported to serve an important role in regulating P-gp expression and MDR (55,56). Notably, activation of the PI3K/Akt pathway can upregulate P-gp in leukemia (56), ovarian cancer (51), liver cancer (57) and lung cancer (55). Compared with PI3K alone, the CDK6-PI3K signal axis synergistically regulates ABCB1 expression more strongly (25). Therefore, the idea of multipathway and multitarget synergistic inhibition of P-gp expression and efficient reversal of MDR was investigated. MEK/ERK is an important downstream signaling pathway of PI3K/Akt. Notably, the MEK/ERK signaling pathway positively regulates P-gp expression, and mediates resistance to DOX, paclitaxel, oxaliplatin, colchicine and vincristine (21,55). Wnt/ β -catenin, which regulates the high expression of P-gp in colon cancer, HCC and leukaemia, is another major signaling

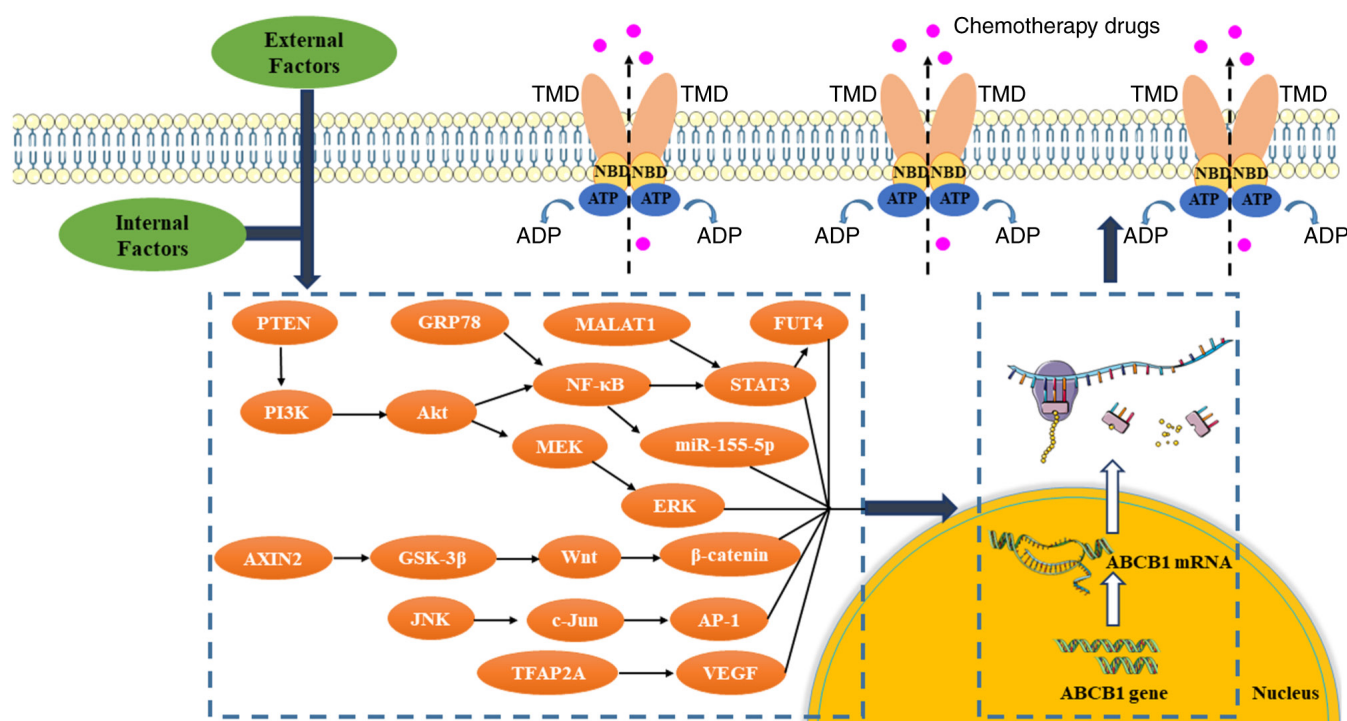


Figure 3. External and internal factors activate or inhibit some signaling pathways, thus upregulating P-gp expression and promoting chemotherapy drug resistance. MDR, multidrug resistance; P-gp, P-glycoprotein; NBD, nucleotide-binding domains; TMD, transmembrane domain.

pathway associated with P-gp-mediated MDR. Moreover, the MALAT1/STAT3/fucosyltransferase 4 (FUT4) (58), JNK/c-Jun/AP-1 (59) and PTN/β-catenin axes (60) are involved in regulating P-gp expression and mediating MDR.

In conclusion, the expression of P-gp is the result of the combined action of several signaling pathways. The discovery of these signaling pathways and regulatory molecules could clarify the role of P-gp and aid in identification of its inhibitors. These signaling pathways and regulatory molecules that promote P-gp expression and MDR can be used as potential targets to reverse chemotherapy resistance; however, no related inhibitors are currently used in clinical chemotherapy. In basic research, direct or indirect inhibition of a target can appropriately alleviate numerous drug resistance phenomena. The future application of these targeted inhibitors in clinical treatment may alleviate chemotherapy resistance and restore the therapeutic effect of chemotherapy drugs.

4. Reversing MDR by inhibiting P-gp

Inhibition of the efflux pump, which can be divided into noncompetitive inhibition and competitive inhibition according to the mechanism, is a direct way to solve MDR induced by P-gp.

Noncompetitive inhibition. Noncompetitive inhibition means that the inhibitor does not compete with the chemotherapeutic agent as a substrate for binding P-gp. There are a number of natural products (61–63) that have been reported as noncompetitive inhibitors of P-gp. Acetylshikonin and acetoxyisovalerylshikonin, which are shikonin derivatives, may be noncompetitive inhibitors of MDR-related transport proteins. They can inhibit

ABCB1, BCRP and MRP2 independent of concentration to increase the accumulation of daunorubicin in carcinoma cells and chemotherapy sensitivity (62). Phytic acid, a natural phosphorylated inositol, can also noncompetitively suppress P-gp; this may be related to reduced P-gp ATPase activity and altered conformations of the P-gp molecule (61). A previous study reported that (±)-30-O, 40-O-dicynnamoyl-cis-kellactone, a derivative of (±)-praeruptorin A, noncompetitively inhibits P-gp-mediated DOX efflux by changing the conformation of P-gp and inhibiting ATPase activity (63).

Some synthetic substances can also be used as noncompetitive inhibitors to inhibit P-gp. Quaternized thiourea main-chain polymer, which is not a substrate for P-gp, has been shown to induce DNA damage and overcome P-gp-associated tumor MDR (64). The novel microtubule inhibitor 5-(4-ethoxy phenyl)-1-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazol-3-amine (YAN), which is not a substrate of P-gp, enhances the cytotoxicity of paclitaxel in NSCLC by decreasing the expression and efflux activity of P-gp (65).

It can be concluded from the aforementioned reports that noncompetitive inhibitors do not bind to the efflux substrate binding pockets of P-gp. However, they may combine with other domains of P-gp to affect its conformation. This principle is similar to the application of allosteric regulators that do not bind to the active site of target proteins to induce protein conformational changes.

Competitive inhibition. Competitive inhibitors binding to P-gp hinder P-gp-drug binding and P-gp-mediated efflux pathways. This method of replacing the drug with another substance as the target of efflux significantly increases the intracellular concentration of the drug.

Small molecule targeted drugs branebrutinib (66), pyrazolo[3,4-d]pyrimidines (67), almonertinib (68) and ribociclib (69) may be potential inhibitors of P-gp. They can compete with P-gp while exerting their own tumor-killing effects, thereby improving chemotherapy sensitivity. This means that there is a dual antitumor effect of chemotherapy combined with targeted therapy. Almonertinib can bind to the TMD of P-gp, whereas ribociclib and branebrutinib interact with the substrate-binding site of P-gp.

As well as existing drugs, a number of natural products have also been shown to inhibit P-gp. Wilforine (14), betulin (70), betulinic acid (71) and lathyrane diterpenes (72), which are terpenoids, all competitively inhibit P-gp efflux activity and overcome MDR. Wilforine may bind to residues of P-gp, such as Leu884, Lys887, Thr176 and Asn172 (14). Betulin tightly binds to the TMD region of P-gp (70). Glabridin (73) and 5-hydroxy-7,8-dimethoxyflavanone (74), which are flavonoid compounds, have also been proven to competitively inhibit P-gp and to increase the accumulation of chemotherapy drugs. Notably, 5-hydroxy-7,8-dimethoxyflavanone may slightly change the conformation of P-gp. Min *et al* (75) proposed that emodin, which is an anthraquinone derivative, can competitively bind to the R site of P-gp to inhibit the efflux function of P-gp and reduce the resistance to DOX. Voacamine, an alkaloid, has been validated as a substrate of P-gp, which was revealed to competitively inhibit the P-gp-mediated export of paclitaxel in ovarian cancer (76). Due to the development of computer simulation techniques and protein structure prediction, precise binding sites of these substances to P-gp have been reported. For the exploration of competitive inhibitors of P-gp, there is a large library of active compounds in natural products. Compared with curcumin, the synthesized dimethyl curcumin pyrazole derivatives with N-p-phenylcarboxamide substitution have higher binding affinity for P-gp and can effectively reverse MDR of chronic myeloid leukaemia to DOX (77). Further modification of natural products enhances the inhibition of P-gp while reducing side effects. This is a future direction for the study of natural products as lead compounds for P-gp inhibition.

The sensitivity of adrenocortical carcinoma to mitotane, DOX, etoposide, cisplatin and streptozotocin can be significantly enhanced by verapamil and tariquidar, which are known as competitive P-gp inhibitors and nontransporter P-gp inhibitors (78). DHW-221, a dual PI3K/mTOR inhibitor, has also been found to bind P-gp to competitively inhibit efflux function and downregulate P-gp (15). The triazolo[1,5-a]pyrimidine derivative WS-716 (79), some 1,4-substituted arylalkyl piperazine derivatives (80), pyrimidine aminobenzene derivatives (81), 5-phenylfuran derivatives characterized by alkyl-substituted phenols and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (82), and the 4-indolyl quinazoline derivative YS-370 (83) have been reported to be potential P-gp competitive inhibitors. They block substrate efflux only by binding to P-gp, but do not affect P-gp expression. The inhibitory activity of most synthetic compounds is an accidental discovery distinct from their initial pharmacological action. However, the initial pharmacological action on patients cannot be ignored as a potential side effect; this may hinder the use of existing drugs to inhibit P-gp.

At present, most recognized P-gp inhibitors are competitive inhibitors. High-affinity compounds that can be pumped

out of the cell as P-gp substrates have the potential to reverse P-gp-associated MDR as competitive inhibitors. However, it is necessary to consider the physiological activity of these compounds on the body, which makes it difficult to use competitive inhibitors in clinical MDR. The application of computer aided simulation technology has significantly improved the screening efficiency of P-gp competitive inhibitors and provided the basis for protein conformation binding in biological experiments.

Uncertain inhibition. Aside from definite competitive and noncompetitive inhibitors, a number of substances that have not been demonstrated to inhibit the efflux activity of P-gp in a clear way can also increase the sensitivity to chemotherapy drugs in certain experiments. According to the source, inhibitors with uncertain mechanisms can be divided into chemically synthesized substances and natural products.

Although it has been reported that decitabine upregulates P-gp expression in resistant cells, it has been found that the drug sensitivity of hematomas and solid tumors with high P-gp expression could be restored by decitabine through activation of the MAPK signaling pathway and inhibition of the efflux pump activity of P-gp (84). Methoxypolyethylene glycol (MPEG)-glycine-quinidine conjugates, which couple MPEG to quinidine via a glycine linker, can also inhibit P-gp in resistant cancer cells (85), and enequidar, a gut-specific P-gp inhibitor, reduces DOX efflux by inhibiting P-gp activity (86).

There are more studies on natural P-gp inhibitors than synthetic P-gp inhibitors. Celastrol has two possible antitumor drug resistance targets, the sarcoplasmic/endoplasmic reticulum Ca²⁺-ATPase (SERCA) pump and P-gp. The sensitivity to chemotherapy drugs can be increased by celastrol, which simultaneously inhibits SERCA to induce autophagy in resistant tumor cells and inhibits the efflux pump function of P-gp (87). Naringenin and dihydrokaempferol extracted from *Pistacia integerrima* can bind to the hydrophobic pocket of P-gp; therefore, naringenin and dihydrokaempferol may be used to reverse MDR by inhibiting the activity of P-gp (88). Moreover, it has been reported that *Camellia sinensis* non-fermentative extract Noviphenone can overcome Adriamycin resistance by inhibiting the activity of P-gp instead of its expression levels (89). The sensitivity to DOX can be restored in paclitaxel-resistant HepG2 and DOX-resistant colon-26 cells without influencing P-gp expression when the cells were treated with the 50% ethanol extract of *Azadirachta indica*, thus it has been inferred that the 50% ethanol extract of *A. indica* can inhibit the activity of P-gp based on the accumulation of the substrate rhodamine 123 (Rh-123) (90).

Antibodies against ABCB1 seem to be the most direct and targeted way to inhibit the activity of ABCB1. Monoclonal antibody (mAb) ABCB1-modified chitosan nanoparticles loaded with gefitinib and the autophagy inhibitor chloroquine have been prepared to overcome acquired EGFR-TKI resistance. The binding of mAb-ABCB1 to receptor (P-gp) suppresses the efflux pump activity of ABCB1, leading to the accumulation of chemotherapeutics (91).

Compared with competitive and noncompetitive inhibitors, uncertain inhibitors can suppress the efflux activity of P-gp without clear mechanisms and are therefore not considered safe candidates. Studies have shown that these inhibitors do

not affect the expression of P-gp. Understanding the mechanism of action of uncertain inhibitors is the key to promote their clinical application.

5. Reversing MDR by inhibiting P-gp expression

RNA interference

lncRNAs. lncRNAs are a class of noncoding RNAs that are involved in intracellular regulation, including the function of overcoming MDR caused by P-gp (Table I).

The overexpression of some lncRNAs can directly or indirectly inhibit P-gp-mediated MDR. lncRNA-GAS5 can directly bind to miR-221-3p and inhibit its expression, the downregulation of which inhibits Dickkopf-related protein (DKK)2 and then activates the Wnt/ β -catenin signaling pathway; ultimately, P-gp expression is reduced in DOX-resistant breast cancer cells (92). In methotrexate-resistant osteosarcoma cells, miR-200c inhibition can upregulate the expression of lncRNA LUCAT1 and P-gp. Upregulation of lncRNA LUCAT1 promotes P-gp expression and P-gp-mediated MDR (93). Knockout of some lncRNAs can also reverse MDR. The expression of colorectal neoplasia differentially expressed (CRNDE) in drug-resistant acute myeloid leukemia cells is directly proportional to the expression of ABCB1 and the sensitivity to Adriamycin has been reported to be enhanced after lncRNA CRNDE knockout. These results may be related to the inhibition of Wnt/ β -catenin pathway by lncRNA CRNDE knockout (94). Furthermore, the expression of ABCB1 is reduced when lncRNA LINC00152 is knocked down, which can increase the chemosensitivity of epithelial ovarian cancer cells to cisplatin (95).

miRNAs. miRNAs are another type of non-coding RNA associated with tumors. These single-stranded RNA molecules can bind to mRNA to regulate gene expression. In recent years, the regulatory role of miRNAs in tumor resistance has gradually attracted attention (Table I).

miRNAs alleviate chemoresistance mainly by directly (96,97) or indirectly (43,60) downregulating P-gp in various types of cancer. It has been reported that miR-495 (96) and miR-491-3p (97) can bind to two sites on the 3'-untranslated region (UTR) of ABCB1 mRNA, thereby inhibiting the expression of ABCB1 and sensitizing cancer cells to chemotherapeutic drugs. The high expression of hsa-miR-34a-5p in gastric cancer cells can inhibit uracil resistance by directly binding to the 3'-UTR of sirtuin 1 (SIRT1), and downregulating SIRT1, P-gp and MRP1 (43).

Numerous studies have shown that the expression of miRNAs in cancer tissues is associated with the levels of P-gp. It has been reported that upregulation of miR-381 (98), miR-34a (99), miR-451 (100), miR-149 (101) and miR-495 (96) can significantly reduce P-gp expression, thereby enhancing the sensitivity of cancer tissues to chemotherapeutic drugs. A retrospective clinical study reported the negative association between miR-200c and the expression of P-gp in gastric cancer tissue. miR-200c overexpression and P-gp downregulation were shown to reverse MDR by increasing drug sensitivity and predicted a better prognosis in patients with gastric cancer (102). The overexpression of miR-122, which has been reported as a negative regulator, can also inhibit the Wnt/ β -catenin signaling pathway and further suppress ABCB1

expression (103). A previous study revealed that there are a number of miRNAs (miR-204-5p, miR-139-5p, miR-29c-5p, miR-551b-3p, miR-29b-2-5p and miR-204-3p) that are specific to lung cancer cells with P-gp-mediated resistance and extracellular vesicles. These miRNAs are likely markers of MDR or key molecules that could be used to overcome P-gp-mediated MDR (104). It has also been reported that miR-205 (24) and miR-29a (105) significantly inhibit P-gp expression by upregulating protein tyrosine phosphatase, thereby enhancing the sensitivity of cancer tissues to DOX.

In addition to the association between the overexpression of miRNAs and the downregulation of P-gp, downregulation of certain miRNAs can also inhibit P-gp expression and MDR through complex signaling pathways. The chemoresistance of MDR leukaemia cells can be attenuated by the loss of miR-1246 via negatively regulating axis inhibition protein 2 and glycogen synthase kinase-3 β to inactivate the Wnt/ β -catenin pathway and suppress P-gp expression (106).

Several miRNAs that inhibit P-gp expression have been identified; however, the expression of P-gp is not the result of a single miRNA. Although miRNAs do not translate proteins, they are involved in regulating P-gp through a variety of signaling pathways.

siRNAs. siRNAs are short non-coding RNAs that can regulate gene expression in the body (107). siRNA-ABCB1 (si ABCB1) targets ABCB1 mRNA to form a double-stranded RNA and hinder the translation of ABCB1 mRNA, decreasing P-gp expression and enhancing chemotherapy sensitivity. Studies on si ABCB1 in tumor resistance have mainly focused on the effect of si ABCB1 delivered by different delivery systems in reversing MDR (108) and the therapeutic effect of siABCB1 in combination with different drugs (109-111).

There have been numerous research achievements regarding the delivery of siRNAs and other materials via nanoparticles or nanocarriers (109,112,113). Liu *et al* (112) prepared a targeted nanoplateform based on biodegradable boronic acid modified ϵ -polylysine to co-deliver P-gp siRNA, Bcl-2 siRNA and DOX. In breast cancer, compared with P-gp siRNA, Bcl-2 siRNA and/or DOX alone, the combined application of P-gp siRNA, Bcl-2 siRNA and DOX supported by nanocarriers has a stronger antitumor effect and ABCB1 gene-silencing effect (112). Wang *et al* (109) designed a biomimetic lipid/dextran hybrid nanocarrier with a diameter of ~100 nm. In this nanocarrier, the anionic si ABCB1 and the hydrophobic drug paclitaxel were loaded into the cationic lipid shell and the hydrophobic internal core of the hybrid nanocarriers, respectively, in order to improve the effect of paclitaxel. In another previous study, a multifunctional polymeric nanoparticle called Py-TPE/siRNA@PMP was loaded with paclitaxel and si ABCB1; this nanoparticle drug delivery system has been shown to enhance chemotherapy sensitivity in ovarian cancer (113).

As well as nanoparticles, there are other types of drug delivery systems. An EphA10-mediated pH-sensitive lipoplex has been developed to co-deliver ABCB1-targeting siABCB1 and DOX (114). In another study, a carrier-free system with MDR as the backbone, loaded with cisplatin and divalent copper was constructed to treat drug-resistant tumors (110).

Developments in the field of materials have improved the delivery of siRNAs in cells. The use of materials to deliver chemotherapeutic drugs and siRNA at the same time allows

Table I. Examples of RNA molecules reversing P-gp-related chemotherapy resistance.

A, lncRNAs					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Chen, 2020	lncRNA-GAS5	Breast cancer	Adriamycin	Regulating miR-221-3p/DKK2 axis and Wnt/ β -catenin/ABCB1 pathway	(92)
Han, 2018	lncRNA LUCAT1	Osteosarcoma	Methotrexate	Regulating miR-200c/ABCB1 pathway	(93)
Kang, 2020	lncCRNDE	Acute myeloid leukemia	Adriamycin	Inhibiting Wnt/ β -catenin pathway and P-gp expression	(94)
Zou, 2019	lncRNA LINC00152	Ovarian cancer	Cisplatin	Inhibiting P-gp expression	(95)
B, miRNAs					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Zou, 2017	miR-495	Ovarian cancer, gastric cancer	DOX, taxol	Inhibiting P-gp expression by binding to the 3'-UTR of ABCB1	(96)
Zhao, 2017	miR-491-3p	Hepatocellular Carcinoma	DOX, vinblastin	Inhibiting P-gp expression by binding to the 3'-UTR of ABCB1	(97)
Deng, 2021	hsa-miR-34a-5p	Gastric cancer	5-Fu	Inhibiting expression of SIRT1 and P-gp by binding to the 3'-UTR of SIRT1	(43)
Yi, 2019	miR-381	Breast cancer	Cisplatin	Directly inhibiting ABCB1 expression	(98)
Zheng, 2019	miR-34a	Hepatocellular carcinoma	DOX	Possibly inhibiting P-gp expression by regulating p53 expression	(99)
Wei, 2020	miR-451	Bladder cancer	Adriamycin	Inhibiting P-gp expression	(100)
Kenworthy, 2018	miR-149	Mesothelioma	Taxane	Inhibiting P-gp expression	(101)
Cao, 2019	miR-122	Hepatocellular carcinoma	Oxaliplatin	inhibiting Wnt/ β -catenin pathway and P-gp expression	(103)
Wang, 2022	miR-200c	Gastric cancer	Vincristine	Inhibiting P-gp expression	(102)
Sousa, 2020	miR-204-5p	Lung cancer	DOX	Unreported	(104)
Sousa, 2020	miR-139-5p	Lung cancer	DOX	Unreported	(104)
Sousa, 2020	miR-29c-5p	Lung cancer	DOX	Unreported	(104)
Sousa, 2020	miR-551b-3p	Lung cancer	DOX	Unreported	(104)
Sousa, 2020	miR-29b-2-5p	Lung cancer	DOX	Unreported	(104)
Sousa, 2020	miR-204-3p	Lung cancer	DOX	Unreported	(104)
Xie, 2021	miR-1246	Leukemia	Adriamycin	Inhibiting AXIN2/GSK-3 β /Wnt/ β -catenin pathway and P-gp expression	(106)
Li, 2022	miR-205	Liver cancer	DOX	Regulating PTEN/PI3K/Akt pathway and P-gp expression	(24)
Shi, 2020	miR-29a	Colon cancer	DOX	Regulating PTEN/PI3K/Akt pathway and P-gp expression	(105)

Table I. Continued.

C, siRNAs	First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
	Peng, 2022	si ABCB1	Breast cancer	DOX	Silencing ABCB1 gene	(154)
	Liu, 2022	si ABCB1, siBcl-2	Breast cancer	DOX	Silencing ABCB1 gene	(112)
	Wu, 2021	si ABCB1	Ovarian cancer	Paclitaxel	Silencing ABCB1 gene	(113)
P-gp, P-glycoprotein; lncRNA, long non-coding RNA; miRNA, microRNA; siRNA, small interfering RNA; MDR, multidrug resistance.						

both agents to be of maximum benefit. If the modified material can be delivered to the target tumor, it will greatly attenuate the downregulation of P-gp in normal tissue and the side effects of chemotherapy.

Drugs that inhibit P-gp expression

Chemically synthesized products. In the process of exploring tumor MDR, a number of chemically synthesized products have been detected to inhibit tumor MDR. Studies conducted in recent years have shown that some anticancer and non-anticancer drugs can downregulate P-gp, enhance chemosensitivity and rescue tumor MDR.

According to a previous study, hypoxia increases HIF1 α expression resulting in P-gp overexpression and NSCLC MDR. By contrast, the HIF1 α inhibitor LW6 can attenuate cisplatin MDR by downregulating P-gp (20). A novel platinum complex can also effectively alleviate cisplatin resistance by inhibiting the expression of P-gp (115). Ribociclib, a CDK4/6 inhibitor, inhibits P-gp-mediated DOX resistance by downregulating the expression and efflux activity of P-gp (69). The small molecule targeted inhibitors sorafenib and apatinib also inhibit P-gp expression and MDR while inducing anticancer effects (116). The killing effect of these drugs may cause tumors to lose the self-protection mechanism of chemotherapy-induced P-gp overexpression.

LSS-11, a novel naphthalimide derivative-based topoisomerase inhibitor, may reduce paclitaxel resistance in A549 lung cancer cells through two different underlying pathways. One of the mechanisms is that it could hinder the binding of STAT3 to the ABCB1 promoters downregulating P-gp (117). A novel microtubule inhibitor, YAN, can inhibit the resistance of NSCLC to paclitaxel by inhibiting the expression of P-gp (65). BAY-1082439, a chemical molecule undergoing phase I clinical trials in patients with advanced cancer, can efficiently inhibit the expression of P-gp and BCRP by selectively inhibiting PI3K 110 α and 110 β , and slightly suppress the efflux effect of P-gp and BCRP (118). A tumor-targeted anticancer agent, FFCLB, covalently linked by the delocalized lipophilic cation FF and CLB, inhibits P-gp expression, thereby increasing the intracellular concentration and cytotoxicity of DOX (119).

According to the aforementioned results, a number of drugs or their derivatives used to treat other diseases can inhibit P-gp expression and reverse chemotherapy resistance. It may be hypothesized that there is an intersection between the signaling pathway these drugs originally interact with to treat disease and the signaling pathway that regulates P-gp expression. Although these drugs can overcome P-gp-mediated chemotherapy resistance, their originally discovered effects are not negligible. However, the combination of small molecule targeted drugs with inhibitory activity and chemotherapy drugs may play a dual role in cancer suppression.

Natural products. In the search for antitumor molecules to combat tumor resistance, screening of natural products may yield safer options than screening chemical compounds. To date, a variety of natural product-derived compounds (120) and plant extracts (121) have been shown to inhibit ABCB1 and reverse tumor MDR *in vitro* and *in vivo*. These research objects can be roughly divided into flavonoids, alkaloids, coumarins, saponins, lignans, phenolic acids and terpenes. The present review summarized these natural products that reverse tumor drug resistance by inhibiting ABCB1 expression (Table II).

Table II. Examples of natural products reversing P-gp-related chemotherapy resistance.

A, Flavonoids					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Kong, 2020	Hesperetin	Lung cancer	Cisplatin	Inhibiting NF- κ B pathway and P-gp expression	(124)
Sui, 2021	Cajanol	Ovarian cancer	Paclitaxel	Inhibiting PI3K/Akt/NF- κ B pathway and P-gp expression	(51)
Qin, 2022	Luteolin	Osteosarcoma	Cisplatin and DOX	Upregulate miR-384, inhibiting PTN/ β -catenin axis and P-gp expression	(60)
Wang, 2018	Icariin	Osteosarcoma	DOX	Inhibiting P-gp expression	(127)
Satonaka, 2017	(-)-Epigallocatechin-3-gallate	Liver cancer	DOX	Inhibiting PI3K/Akt and MEK/ERK pathway, P-gp expression	(57)
La, 2019	(-)-Epigallocatechin gallate	Colorectal cancer	5-Fu	Inhibiting GRP78/NF- κ B/miR-155-5p/ABCB1 pathway and P-gp expression	(125)
Tang, 2017	Epigallocatechin gallate	Gastric cancer	5-Fu	Inhibiting TFAP2A/VEGF pathway and P-gp expression	(42)
Qian, 2019	Glabridin	Breast cancer	Paclitaxel, DOX	Inhibiting P-gp expression and P-gp ATPase activity, competitively inhibiting the efflux activity of P-gp	(73)
Teng, 2021	5-Hydroxy-7,8-dimethoxyflavanone	Oral cavity carcinomas	Vincristine	Competitively inhibiting the efflux activity of P-gp	(74)
B, Alkaloids					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Huang, 2017	Cepharanthine	Ovarian cancer	Paclitaxel	Inhibiting PI3K/Akt pathway and P-gp expression	(132)
Zhou, 2017	Cepharanthine	Esophageal squamous cell carcinoma	Cisplatin	Activating JNK/p53 pathway and inhibiting P-gp expression	(129)
Zhou, 2022	Tetrandrine	Leukemia	Daunorubicin	Inhibiting the efflux activity and expression of P-gp	(130)
Qian, 2021	Berberine	Breast cancer	DOX	Inhibiting the efflux activity and expression of P-gp	(131)
Liu, 2020	Nuciferine	Lung cancer, bowel cancer	Paclitaxel, DOX, docetaxel, daunorubicin	Inhibiting PI3K/AKT/ERK pathway and activation of Nrf2 and HIF-1 α , P-gp expression	(55)
Quarti, 2021	Piperine	Leukemia	Vincristine	Inhibiting P-gp expression	(134)
C, Coumarins					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Wang, 2011	Archangelicin	Leukemia	DOX	Inhibiting the function and expression of P-gp	(135)
Wang, 2016	Osthole	Leukemia	DOX	Inhibiting PI3K/Akt pathway and expression of P-gp	(56)
Shen, 2006	(\pm)-30-O, 40-O-dicynnamoyl-cis-kellactone	Hepatocellular carcinoma, leukemia	DOX	Noncompetitively inhibiting the efflux activity of P-gp	(63)

Table II. Continued.

D, Saponins					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Huang, 2012	Astragaloside II	Hepatic cancer	5-Fu	Inhibiting the efflux activity and expression of P-gp via phosphorylation of ERK1/2, p38 and JNK	(140)
Wang, 2017	Astragaloside IV	Hepatic cancer	5-Fu	Inhibiting JNK/c-Jun/AP-1 pathway and P-gp expression	(59)
Liu, 2018	Ginsenoside Rh2	Colorectal carcinoma	5-Fu	Inhibiting P-gp expression	(142)
Liu, 2018	20(S)-ginsenoside Rg3	Lung cancer	Cisplatin	Inhibiting P-gp expression	(143)
E, Lignans					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Sadava, 2013	Silibinin	Small cell lung carcinoma	Etoposide, DOX	Possibly inhibiting P-gp expression	(144)
Dobiasová, 2020	Silibinin stereoisomer B	Ovarian cancer	DOX	Inhibiting P-gp expression and P-gp ATPase activity	(145)
Dobiasová, 2020	2,3-Dehydrosilibinin A	Ovarian cancer	DOX	Unreported	(145)
Zhang, 2018	Schisandrin A	Breast cancer	DOX	Inhibiting the P-gp, NF- κ B and Stat3 pathway, and inhibiting P-gp expression	(146)
E, Phenolic acids					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Liao, 2020	Rosmarinic acid	Non-small cell lung cancer	Cisplatin	Possibly activating JNK phosphorylation and inhibiting P-gp expression	(147)
Muthusamy, 2019	Ferulic acid	Oral cavity carcinomas	DOX, vincristine	Inhibiting PI3K/Akt/NF- κ B pathway and P-gp expression	(148)
Gao, 2021	Curcumin	Colon cancer	5-Fu	Inhibiting Wnt/ β -catenin pathway and P-gp expression	(23)
Teng, 2020	Caffeic acid	Oral cavity carcinomas	DOX	Competitively inhibiting efflux activity of P-gp	(155)
F, Terpenes					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Oh, 2020	Cordycepin	Bladder cancer	Cisplatin	Inhibiting PI3K pathway, ETS-1 phosphorylation and P-gp expression	(149)
Ma, 2020	Asiaticoside	Hepatocellular carcinoma	DOX, paclitaxel, colchicine, vincristine	Inhibiting PI3K/Akt and MAPK/ERK pathway	(156)

Table II. Continued.

F, Terpenes					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Ding, 2022	Alantolactone	Lung cancer	Paclitaxel	Inhibiting MALAT1/STAT3/FUT4 axis and P-gp expression	(58)
Ding, 2022	Brevilin A	Lung cancer	Paclitaxel	Inhibiting MALAT1/STAT3/FUT4 axis and P-gp expression	(58)
Chang, 2020	Wilforine	Cervical cancer	DOX	Competitively inhibiting the efflux activity of P-gp	(14)
Laiolo, 2021	Betulin	Leukemia	DOX	Competitively inhibiting the efflux activity of P-gp	(70)
Liu, 2021	Betulinic acid	Breast cancer	Adriamycin, vincristine	Competitively inhibiting the efflux activity of P-gp	(71)
Yang, 2020	Lathyrane diterpenes	Hepatocellular carcinoma	DOX	Competitively inhibiting the efflux activity of P-gp	(72)
G, Quinones					
First author, year	Substance	Tumor type	Corresponding drug	Anti-MDR mechanism	(Refs.)
Mirzaei, 2018	Acetylshikonin	Breast cancer	Daunorubicin	Noncompetitively inhibiting the efflux activity of P-gp	(62)
Mirzaei, 2018	Acetoxysovalerylshikonin	Breast cancer	Daunorubicin	Noncompetitively inhibiting the efflux activity of P-gp	(62)
P-gp, P-glycoprotein; MDR, multidrug resistance.					

Flavonoids. Flavonoids are a class of plant metabolites with a 2-phenylchromone structure that exist widely in nature. A variety of flavonoids have been shown to have antitumor and anti-resistance activities (122). Different structures of flavonoids have different mechanisms of action and inhibitory activities (123).

The NF- κ B signaling pathway is involved in the mechanism by which a variety of natural compound monomers inhibit P-gp expression. Hesperetin, a derivative of hesperidin that is extracted from tangerine peel, has been reported to inhibit tumor growth *in vivo* and to restore the sensitivity of A549 lung cancer cells to cisplatin by inhibiting the NF- κ B signaling pathway and expression of P-gp (124). Cajanol, an isoflavone from pigeon pea, can inhibit the transcription and translation of P-gp through the PI3K/Akt/NF- κ B pathway, and reverse the resistance of ovarian cancer cell lines to paclitaxel *in vitro* and *in vivo* (51). It has also been reported that P-gp expression and P-gp ATPase activity are suppressed by glabridin (73).

The regulation of P-gp expression by various natural products is related to miRNAs (60,125). Luteolin can enhance the sensitivity of osteosarcoma to cisplatin and DOX; it has been reported that luteolin can upregulate miR-384, which indirectly inhibits P-gp expression by negatively regulating the PTN/ β -catenin axis (60).

Additionally, natural products that have been shown to inhibit P-gp expression also include epigallocatechin gallate (42), theaflavin, quercetin, rutin, epicatechin 3 gallate, tamarixetin (126) and icaritin (127).

Alkaloids. *Salvia miltiorrhiza* (128), cepharanthine hydrochloride (129), tetrandrine (130) and berberine (131) can inhibit the expression of P-gp to reverse tumor MDR. Cepharanthine hydrochloride can serve a role in reversing drug resistance in ovarian cancer via inhibiting the expression of ABCB1, and reducing the mRNA and protein expression levels of P-gp, which may be caused by inhibiting the PI3K/Akt signaling pathway (132). Tetrandrine (133), nuciferine (55) and berberine (131) have been reported to increase the intracellular aggregation of chemotherapeutic drugs via their dual inhibitory effects of inhibiting the efflux activity of P-gp and inhibiting the expression of P-gp. Tetrandrine and berberine are isoquinoline alkaloids. Notably, inhibition of P-gp expression by tetrandrine does not occur through the inhibition of ABCB1 transcription (133). Furthermore, inhibition of P-gp expression by nuciferine is regulated by a series of signaling pathways. Nuciferine can effectively inhibit the PI3K/AKT/ERK signaling pathway, and the activation of Nrf2 and HIF-1 α , which can reduce P-gp expression and enhance MDR sensitivity in tumor cells (55). Additionally, the ability of piperine to overcome MDR in leukaemia cells may be related to downregulation of P-gp (134).

Coumarins. Coumarins are a class of aromatic compounds ubiquitous in nature with a benzopyrone structure. Some coumarins have been reported to overcome MDR by inhibiting the activity and expression of P-gp. A previous study revealed that archangelicin can inhibit the function and expression of P-gp, and ultimately reduce the resistance of the leukaemia cell line K562/A02 to DOX (135). Osthole has also been shown to inhibit the expression of P-gp by inhibiting the PI3K/Akt signaling pathway, which can be induced by the uptake and efflux of Rh-123 and the accumulation of DOX (56).

Saponins. Saponins, consisting of sapogenins and sugars, are mainly found in plants. There are a number of types and complex structures of saponins (136). Numerous saponins, including Paris saponin VII (137), ginsenoside Rb1 (138) and sodium aescinate (139), have been reported to inhibit the expression of P-gp and reverse tumor resistance. Astragaloside II has been found to increase the intracellular accumulation of P-gp substrates by inhibiting the efflux pump activity of P-gp. On the other hand, it can also inhibit the expression of ABCB1 and suppress the phosphorylation of ERK1/2, p38 and JNK; these functions facilitate its role in reversing tumor MDR (140). Wang *et al* (141) investigated astragaloside IV and verified that astragaloside IV can inhibit the expression of ABCB1, increase the intracellular accumulation of 5-Fu, and ultimately achieve the goal of inhibiting tumor resistance. In subsequent experiments, it was further confirmed that the specific mechanism by which astragaloside IV inhibits the expression of ABCB1 is by inhibiting the JNK/c-Jun/AP-1 signaling pathway (59). In addition, the activity of ginsenoside Rh2 in reversing tumor resistance may be related to its inhibition of P-gp expression. In a previous study, it was revealed that the expression levels of MRP1, ABCB1, LRP and glutathione S-transferase are negatively correlated with ginsenoside Rh2 (142). In addition to ginsenoside Rh2, 20(S)-ginsenoside Rg3 can also enhance the cytotoxicity of chemotherapy drugs by inhibiting the expression of drug resistance genes (143).

Lignans. Silibinin is considered to be the main bioactive component of silymarin. In a previous report, it was speculated that silibinin increased the chemosensitivity of small cell lung cancer by downregulating P-gp rather than inhibiting the efflux function of P-gp (144). However, in recent years, silibinin stereoisomer B and its derivative 2,3-dehydrosilibinin A have also been found to sensitize ovarian cancer cells to DOX, and silibinin stereoisomer B exhibits dual inhibition of P-gp ATPase activity and P-gp expression (145). Schisandrin A can also inhibit the expression of P-gp by reducing the levels of phosphorylated (p)-I κ B- α (Ser32) and p-Stat3 (Tyr705). Combined with its blocking of P-gp efflux activity, it enhances the sensitivity of MDR breast cancer cells to DOX (146).

Phenolic acids. Rosmarinic acid reverses cisplatin resistance in NSCLC by activating MAPK and thereby inhibiting P-gp expression (147). Ferulic acid has also been reported to enhance the cytotoxicity of DOX and vincristine on MDR cells with high P-gp expression, which is dependent on the PI3K/Akt/NF- κ B signaling pathway to inhibit P-gp expression (148). Curcumin has also been reported to downregulate the expression of P-gp (23).

Terpenes. Terpenoids are widely found in animals and plants, such as essential oils, resins, pigments, hormones and vitamins. Terpenoids have isoprene basic units in their structure. Cordycepin inhibits the expression of ABCB1, thereby enhancing the sensitivity of cisplatin-resistant bladder cancer cells to cisplatin. Cordycepin may inhibit the PI3K signaling pathway and thereby attenuate the phosphorylation of ETS-1 (Thr38), a transcription factor that can activate the ABCB1 promoter after phosphorylation. The reduction in ETS-1 (Thr38) phosphorylation hinders the transcription and expression of ABCB1, downregulates the expression of P-gp and reduces the resistance of bladder cancer cells (149). Alantolactone and brevilin A, which are sesquiterpene lactones,

can inhibit the resistance of lung cancer cells to paclitaxel (58). The mechanism involves the inhibition of MALAT1 expression by alantolactone and brevilin A, the subsequent activation of STAT3 and the upregulation of FUT4, and ultimately the positive reduction of P-gp expression.

These natural products inhibit P-gp expression and reverse chemotherapy resistance by regulating the NF- κ B/STAT3, PI3K/AKT, MEK/ERK and Wnt/ β -catenin signaling pathways. These involved signaling pathways are consistent with those that promote P-gp-related chemotherapy resistance in different tumors. Furthermore, these results confirm that these signaling pathways are important and inhibitors targeting these signaling pathways should be studied.

Biological compounds. In addition to some of their own biological activities, a number of biological compounds in the human body, including proteins, enzymes, nucleic acids, hormones, antibodies and cytokines, have been proven to be effective in antitumor MDR.

Tumor necrosis factor α -induced protein 8-like 2 (TIPE2) is a tumor suppressor that is related to P-gp. P-gp can be inhibited by TIPE2 via inhibiting the TAK1-NF- κ B-AP-1 signaling pathway, thus sensitizing osteosarcoma cells to cisplatin (52). It may be hypothesized that the overall inhibition of tumors by other targets may affect the expression of P-gp in tumors. This seems to confirm the win-win effect of chemotherapy in combination with other treatments. The NF- κ B signaling pathway has an important role in regulating P-gp expression. Melatonin downregulates NF- κ B/P65 expression in the nucleus and disrupts the binding of P65 to the ABCB1 promoter. Melatonin-mediated downregulation of P-gp expression increases the chemosensitivity of diffuse large B-cell lymphoma cells to epirubicin (54). Estrogen 2-methoxyestradiol can interact with cadmium in ovarian cancer to reduce P-gp expression as a potential MDR regulator (150). γ -Tocotrienol inhibits P-gp expression in breast cancer via the NF- κ B signaling pathway (151). The impact of tumors on the body is systemic rather than local and the malignant progression of tumors is accompanied by changes in hormone levels. To overcome P-gp mediated MDR, systemic treatment, such as targeted therapy combined with chemotherapy and targeted therapy combined with immunotherapy, should be considered (1,2).

In addition to these endogenous substances, biologics used to inhibit P-gp in the body are also effective. It has been found that an adenovirus vector carrying DKK3 can augment the antitumor effect of temozolomide in glioblastoma cells by reducing the expression of P-gp, which is associated with inhibition of Akt/NF- (152).

Active substances in humans have better biosafety profiles than those derived from natural products or synthetic compounds. These biological compounds can regulate the expression of P-gp by inhibiting or activating certain signaling pathways and molecules. Therefore, regulation of P-gp expression and chemotherapy resistance can be affected by altering the expression levels or activities of these biological compounds *in vivo* and *in vitro*.

6. Reversing MDR by silencing ABCB1 DNA

The reversal of P-gp-mediated tumor MDR by inhibiting the activity and expression of P-gp has been introduced in

the present review. If these two methods block the intermediate steps of P-gp-mediated tumor resistance, then directly knocking out or silencing the ABCB1 gene can completely inhibit P-gp expression and curb resistance.

CRISPR/Cas9 is an efficient and convenient gene editing technology. It can use single guide RNA (sgRNA) to identify target gene DNA and guide Cas9 endonuclease to cut DNA to achieve gene knockout. Three sgRNAs targeting the fourth and fifth exons of the human ABCB1 gene were designed by Norouzi-Barough *et al* (153). When all three Cas9-sgRNA plasmids were transfected into Adriamycin-resistant cells, the three sgRNAs bound to the target exons of ABCB1 inducing the Cas9 endonuclease to cut the target gene ABCB1. Finally, ABCB1 was knocked out. Low-level expression of P-gp was detected in the experiment, which verified that CRISPR/Cas9 technology successfully knocked down the ABCB1 gene. In addition, the increased sensitivity of ABCB1-knockdown cells to Adriamycin suggested that knocking out drug resistance genes through gene editing may be a new way to solve drug resistance (153). However, how to safely and effectively apply this to the clinical treatment of cancer is a difficult problem to be solved. The urgency of the problem is alleviated by the continual discovery of new drugs.

7. Conclusions and perspective

Chemotherapy drugs inhibit tumor cells by killing them indiscriminately and thus have cytotoxic effects on normal cells, leading to strong side effects. Targeted therapy and immunotherapy have fewer side effects and are emerging therapies for cancer. However, due to the difference in individual immune status, the therapeutic effect of immunotherapy differs significantly among individuals. Differences in the phenotype of targeted genes also limit the use of targeted therapy. Therefore, chemotherapy remains an irreplaceable therapy in cancer treatment.

P-gp upregulation in cancer leads to chemoresistance since P-gp pumps chemotherapeutic agents out of the cell. Multiple signaling pathways, including PI3K/AKT (25), MEK/ERK (21), Wnt/ β -catenin and NF- κ B/STAT3, promote the chemotherapy resistance of various tumor cells. The mechanism of P-gp upregulation is consistent in different tumors (16,20,37,49). Multiple signaling pathways, including PI3K/AKT (37), MEK/ERK (21), Wnt/ β -catenin and NF- κ B/STAT3, promote the chemotherapy resistance of various tumor cells. Notably, the consistent mechanisms in different tumors reduces the burden of exploring ways to overcome P-gp-mediated chemotherapeutic resistance in different tumors.

Currently, the pathways found to reverse P-gp mediated chemotherapeutic resistance can be divided into three categories: Inhibition of the efflux function of P-gp, inhibition of the expression of P-gp and knockdown of the ABCB1 gene. Competitive or noncompetitive inhibition of P-gp efflux function represents the most direct method. This class of inhibitors, which mainly includes natural products and synthetic compounds, impedes the binding of P-gp to chemotherapy drugs by binding to P-gp or changing the conformation of P-gp. Computer-aided simulation technology can be used to screen P-gp inhibitors. Downregulation of P-gp is the way in which most inhibitors act. The

regulation of P-gp expression by natural products, synthetic compounds, RNA and biological compounds in humans involves a variety of mechanisms and molecular targets, such as the PI3K/AKT (51), MEK/ERK, Wnt/ β -catenin and NF- κ B/STAT3 (58) signaling pathways. Numerous small molecule targeted inhibitors not only exert antitumor effects, but also inhibit P-gp expression and MDR, reflecting the increased efficacy of the combination of targeted therapy and chemotherapy. However, compared with inhibition of signaling pathways, direct inhibition of the substrate-binding site and efflux activity of P-gp is more effective in theory. To some extent, some P-gp competitive and noncompetitive inhibitors act in a manner similar to allosteric regulation, regulating protein activity by changing the structure of the protein. At present, there is a complete and feasible development process for allosteric regulators of target proteins. Perhaps the research of P-gp efflux inhibitors can refer to the exploration of allosteric regulators.

In conclusion, the present review describes P-gp-mediated chemotherapeutic resistance and related mechanisms in various types of cancer to alert researchers to the importance of P-gp in chemotherapeutic resistance. It may be possible to explore the related mechanisms to overcome P-gp-mediated chemoresistance. In addition, the present review summarized the active substances that reverse P-gp-mediated chemotherapeutic resistance to provide candidate compounds for screening clinical P-gp inhibitors and lead compounds for the development of new P-gp inhibitors.

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Authors' contributions

YT and FX designed the article. YT, YL, YW and JL participated in the literature search. YT was the major contributor in writing the manuscript. FX and JW participated in manuscript revision. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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